# Failure of epoprostenol (prostacyclin, $PGI_2$) to inhibit platelet aggregation and to prevent restenosis after coronary angioplasty: results of a randomised placebo controlled trial

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**Abstract**

***Objective*—To study the effect of epoprostenol (prostacyclin, $PGI_2$) given before, during, and for 36 h after coronary angioplasty on restenosis at six months and to evaluate the transcardiac gradient of platelet aggregation before and after percutaneous transluminal coronary angioplasty (PTCA) in treated and placebo groups.**

***Design*—Double blind placebo controlled randomised study.**

***Patients*—135 patients with successful coronary angioplasty.**

***Methods*—Intravenous infusion of $PGI_2$ (4 ng/kg/ml) or buffer was started before balloon angioplasty and continued for 36 hours. Platelet aggregation was measured in blood from the aorta and coronary sinus before and after PTCA in each group. Routine follow up was at six months with repeat angiography and there was quantitative assessment of all angiograms (those undertaken within the follow up period and at routine follow up).**

***Presentation of results*—Restenosis rates in treated and placebo groups determined according to the National Heart, Lung and Blood Institute definition IV. Comparison at follow up between the effect of treatment on mean absolute luminal diameter and mean absolute follow up diameter in the placebo group. Comparison of acute gain and late loss between groups.**

***Results*—Of 125 patients available for assessment 23 were re-admitted because of angina within the follow up period. Quantitative angiography showed restenosis in 15 (10 in the $PGI_2$ group and five in the placebo group). Of 105 patients evaluated at six month angiography there was restenosis in nine more in the $PGI_2$ group and 18 more in the placebo group. Total restenosis rates (for patients) were 29·2% for $PGI_2$ and 38·3% for placebo (NS). The mean absolute gain in luminal diameter was 1·84 (0·76) mm in the $PGI_2$ group and 1·58 (0·56) mm in the placebo group ($p = 0·04$); the late loss in the $PGI_2$ group was also greater (0·65 (0·94) mm *vs* 0·62 (0·89) mm (NS) and there was no significant difference in final luminal diameter at follow up between the two groups (1·83 (0·88) mm *v* 1·59 (0·60) mm). The transcardiac gradient of quantitative platelet aggregation increased after PTCA in both groups, indicating that $PGI_2$ in this dose did not affect angioplasty-induced platelet activation. Mean (SD) platelet activation indices in the $PGI_2$ group were pre PTCA aorta 8·4 (4·1) *v* coronary sinus 8·8 (4·0) ($p = 0·001$) and post PTCA aorta 8·9(3·0) *v* coronary sinus 12·9 (5·7) ($p = 0·001$). In the placebo group the values were pre PTCA aorta 7·6 (3·3) *v* coronary sinus 7·4 (3·6) ($p = 0·001$) and post PTCA aorta 7·6(2·8) *v* coronary sinus 11·2(4·3) ($p = 0·001$).**

***Conclusion*—The dose of $PGI_2$ given was designed to limit side effects and as a short-term infusion did not significantly decrease the six month restenosis rate after PTCA. The sample size, which was determined by the original protocol and chosen because of the potency of the agent being tested, would have detected only a 50% reduction in restenosis rate. There was, however, no effect in the treated patients on the increased platelet aggregation seen in placebo group as a result of angioplasty. Angioplasty is a powerful stimulus to blood factor activation. Powerful agents that prevent local platelet adhesion and aggregation are likely to be required to reduce restenosis.**

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Restenosis after angioplasty occurs as a consequence of an over response of the vessel wall to balloon damage. The procedure itself causes considerable damage to the artery[1 2] with loss of endothelial cells and disruption of the intima and media. Experimental models have shown that platelets adhere to the damaged surface within a few minutes.[3 4] Adherence, activation, and $\alpha$ granule release of growth factors for smooth muscle cells are a well recognised sequence[5–8] and smooth muscle cell intimal hyperplasia is acknowledged to be the cause of restenosis in the 70% or so of cases not caused by recoil,[9] as shown by necropsy[10 11] and in atherectomy-retrieved samples from lesions that have restenosed.[12]

A normal endothelium protects against the unwanted interaction between platelets and subendothelial platelet-adhering collagen and

microfibrils. It acts both as a physical and chemical barrier partly through its high concentration of prostacyclin ($PGI_2$) which is the most powerful antiaggregating substance known.[13] $PGI_2$ is concentrated in the endothelial layer[14] and acts by increasing platelet cAMP which in turn inhibits intraplatelet activation metabolic pathways.[15 16] Balloon angioplasty, by removing the endothelial layer, will diminish the concentration of locally produced prostacyclin. Infused into normal volunteers $PGI_2$ has been shown to have antiplatelet effects.[17] Prostacyclin (as epoprastenol, $PGI_2$) therefore seems to be a good candidate for reducing the incidence of restenosis after coronary angioplasty.

We assessed the effect of epoprostenol ($PGI_2$) administered intravenously, during and for 36 hours after PTCA, on quantitatively determined restenosis. Any effect of $PGI_2$ on changes in transcardiac platelet function measured during angioplasty was also evaluated.

## Patients and methods

All patients undergoing angioplasty at the London Chest Hospital were considered for inclusion in the trial, with the exception of those with total coronary occlusion, restenosis, after previous angioplasty, or vein graft lesions. The trial was approved by the ethics committee of the National Heart and Brompton Hospitals.

After formal consent patients were randomly allocated to received either $PGI_2$ infusion, made up in buffer to permit an infusion rate of 4 ng/kg/min, or buffer alone. Patient and operator were blinded to the randomisation group. The $PGI_2$ was made up by the pharmacy department from stored material provided by Wellcome.

### ANGIOPLASTY PROCEDURE

All patients received 300 mg aspirin with their premedication. After a femoral artery sheath was in place, blood pressure was recorded and the infusion was started provided the systolic blood pressure was >110 mm Hg. Heparin 10 000 U and diazepam 5 mg were given via the femoral vein sheath, as was the routine clinical practice. A 7 F NIH catheter was passed via the femoral vein into the coronary sinus in order to obtain blood samples for platelet aggregometry and measurement of 6 keto $PGF_{1\alpha}$ (the stable metabolite of $PGI_2$. Dye visualisation was used to place the catheter as close as possible to the vein draining the target artery (great cardiac vein for the left anterior descending coronary artery; middle or posterior cardiac vein for the circumflex and right coronary arteries). Once the infusion had been running for a minimum of 10 minutes the chosen guiding catheter was placed in the aortic root close to but not engaged in the coronary artery.

### ASSESSMENT OF PLATELET FUNCTION

After 5 ml of blood had been drawn from the coronary sinus catheter, and discarded 4·5 ml was carefully taken into a test tube containing 0·5 ml trisodium citrate (TSC). This was sample CS1. Another 4·5 ml blood sample (designated A1) was taken from guiding catheter in the aortic root (and placed in a further 0·5 ml TSC). The angioplasty was then performed according to operator's choice of wire, balloon, inflation pressure, and inflation times. During this time the coronary sinus catheter was carefully hand flushed with heparinised saline every half hour.

Immediately after established angiographic success, further blood samples were taken as before from the catheter in the coronary sinus (CS2) and from the guiding catheter which had been disengaged from the coronary artery but left close to its origin (A2). All samples were processed within two hours of withdrawal. Samples for 6-keto-$PGF_{1\alpha}$ were stored at −70°C for radioimmunoassay. Samples for aggregometry were transferred to the haematology laboratory, the platelet count was standardised to 200 × $10^9$/l with platelet poor plasma, and analysed without delay. To ensure platelet viability we discarded any samples that could not be measured within 2 h of collection, because of a prolonged PTCA procedure, for example. We assessed aggregability by calculating a dose response curve to ADP[18]—that is, the slope produced by plotting the initial aggregation slope against the log concentration of ADP required to produce that slope for final concentrations of ADP of 20 $\mu$M, 10 $\mu$M, 5 $\mu$M, 2·5 $\mu$M, and 1·25 $\mu$M ADP. The value of the slope produced is the platelet activation index (PAI).[18] Blood concentrations of 6-keto-$PGF_{1\alpha}$ were batch analysed by a radioimmunoassay (Amersham International). The results were expressed as pg/ml.

### TREATMENT ALLOCATION

All patients who had successful angioplasty received active $PGI_2$ or placebo buffer infusion according to their randomisation group for 36 hours after the procedure. The infusion syringes were changed by the pharmacy department every 10 hours because after this time $PGI_2$ activity lessens. Unless contraindicated all patients also received a nitrate infusion (2 mg/h Isoket) and heparin (1000 U/h), both for 24 h, as was unit policy at that time. Any symptoms during this time were recorded, particularly bradycardia, hypotension, flushing, or nausea. Patients were discharged on aspirin, the dose being determined according to the physicians' usual choice. Other drugs given on discharge were nitrate and/or calcium antagonist, again as chosen by the physician.

### FOLLOW UP EVALUATION

Patients were routinely admitted six months after angioplasty and performed an exercise stress test (modified Bruce protocol). A full history was taken to highlight any symptoms during the previous six months as well as the current cardiac status. Angiography was

repeated in views identical with those used at the previous angioplasty.

Patients who were admitted *within* the six month follow up and who gave a history of angina that was thought by their physician to justify angiography were considered to have reached an end point of the study. For ethical reasons none of the patients who did not have angiographic restenosis within the six month follow up period had further angiography at six months.

QUANTITATIVE ANGIOGRAPHY

All angiograms obtained at routine six month follow up and those taken during early admission within the six months were analysed by quantitative videodensitometry. This was done without knowledge of the patient's randomisation group. The Vangard XR70 system was used to generate absolute diameters for both normal artery reference segments and for regions of maximal stenosis. Percentage stenotic narrowing was also calculated. Where possible orthogonal views were used, although this was not regarded as essential when the artery was foreshortened in the orthogonal view or where there was overlap, as was frequently the case with mid or distal light coronary artery lesions. The normal artery reference segment was taken to be as close as possible to the stenotic region but outside any area of normal artery involved in balloon inflation. To allow for vessel tapering, the diameter of the normal artery segment both proximal and distal to the stenosis was measured and the mean calculated. All measurements were recorded during a diastolic frame with the coronary arteries maximally filled. All measurements (normal proximal, normal distal, region of maximum severity) were taken three times and a mean value calculated. Results were obtained for stenotic lesions and normal arteries before and after angioplasty and from the follow up angiogram, whether at planned six month admission or from an earlier angiogram. The Vangard XR70 system has been extensively assessed against phantoms and postmortem coronary arteries[19 20] as well as against other quantitative systems such as the CAAS system[21] and has been shown to provide an accurate measurement of absolute diameter.

DATA ANALYSIS

The data were analysed as follows:

- Comparison of restenosis rates between $PGI_2$ and control groups.
- Comparison of absolute mean follow up luminal diameter (mm) in $PGI_2$ treated patients compared with control value.
- Comparison of absolute and relative gain and absolute and relative loss in $PGI_2$ and control groups.

RESTENOSIS DEFINITION

The restenosis rates in the two groups were determined according to the NHLBI IV definition which is based on a comparison between the stenotic region and a normal reference segment (restenosis being defined by loss of a 50% percentage gain). This definition has been shown to correlate with other relative definitions such as >50% at follow up.[22]

Relative definitions have their detractors, and we, like others, have used other means of comparing the effect of treatment on angiographic outcome after angioplasty. For example, we plotted the absolute diameter against the cumulative incidence for the treated and placebo group before, immediately after angioplasty, and at follow up.[23]

Recent evidence has indicated that restenosis is a continuous variable.[24] Therefore mean absolute diameter at follow up in the placebo group was quantitatively compared with absolute mean diameter for $PGI_2$ group, ensuring that we took account of any differences between groups in absolute diameters PTCA before and after. Relative loss and relative gain were thus calculated for the two groups.

STATISTICAL METHODS

*Sample size*

Sample size is dependent on the expected outcome required for the agent being tested. When this trial was set up, $PGI_2$ was known to be a powerful antiplatelet agent. None the less we thought its routine use was unlikely because of known powerful side effects unless it could be shown to have a significant impact on restenosis (that is, a 50% reduction in restenosis rates or in the loss of minimal luminal diameter). The mean restenosis rate calculated from the control population of 23 other trials was 36%. Power calculations at the onset of this study thus indicated that if we were to achieve our aim (to reduce the restenosis rate to about 18%) 73 patients would be required in each group to detect this difference. (85% power, $2p = 0{\cdot}05$).

To assess further the *effect of treatment* (rather than to compare restenosis rates), we have considered that the mean absolute difference in placebo group luminal diameter from immediately after PTCA to follow up was likely to be about 0·7 mm[25] with an approximate standard deviation of about 0·5 mm. To show a reduction to 0·35 mm in the difference produced by treatment would also require 73 patients/group.

*Trial commencement*

Because this was a study of the effect of a treatment on subsequent recurrence after successful angioplasty, the trial was deemed to have started when the patient had completed the 36 h infusion after successful angioplasty.

*Comparison of quantitative angiographic data*

Absolute diameters between and within the groups were compared by a non-parametric test (Mann Whitney U).

*Platelet function tests*

We used paired *t* tests to compare the platelet activation index in the samples taken before

and after angioplasty from the coronary sinus with those taken from the aorta.

*End points*

The end points for this trial were (*a*) cardiac death, (*b*) a history of angina sufficient to warrant admission leading to cardiac catheterisation, (*c*) admission with angina and electrocardiographic evidence of ischaemia if intervention (PTCA or coronary surgery) was undertaken without prior cardiac catheterisation, and (*d*) six month follow up angiogram.

*Presentation of results*

The results are presented as number (%) in each group defined as having restenosis (see above), as mean absolute values at follow up, and as acute relative gain versus late relative loss. Since the treatment being tested was a systemic treatment and might thus be expected to benefit all dilated lesions, the groups were analysed initially as patients rather than as lesions and a patient was considered to have restenosed when at least one lesion had restenosed.

## Results

A total of 155 patients were randomised: 76 to $PGI_2$ (in buffer 4 ng/kg/h for 36 h) and 79 to placebo (buffer alone for 36 h). Angioplasty was unsuccessful because of failure to cross the lesion with a wire or balloon in seven of those initially randomised to active treatment and eight in controls. Of the 69 patients in $PGI_2$ group who went back to the ward with an infusion running, two suffered chest pain and ECG changes sufficient to warrant recatheterisation within the first 36 h (one at 0·5 h and one at 2 h: both had repeat angioplasty). Of the 71 patients in the placebo group, three required recatheterisation for chest pain and ECG symptoms within 36 h (one at 1 h, one at 75 min, and one at 5 h: all had repeat angioplasty. No acute deaths occurred. This left 67 patients in the prostacyclin arm of the study and 68 patients in the placebo arm.

SIDE EFFECTS DURING THE INFUSION PERIOD

Table 1 shows the incidence of reported side effects in the two groups during the infusion period. Flushing and headache are subjective effects. Hypotension was defined as a 20% reduction in previous systolic blood pressure and bradycardia as a heart rate <50 beats/min.

*Table 1 Symptoms during the first 24 hours after the start of infusion.*

| Symptom | $PGI_2$ (n = 67) | Placebo (n = 68) |
|---|---|---|
| Flushing | 8 | 4 |
| Headache | 9 | 6 |
| Nausea | 2 | 0 |
| Vomiting | 4 | 1 |
| Hypotension* | 3 | 1 |
| Bradycardia† | 3 | 1 |
| Nodal rhythm | 3 | 2 |
| Intravenous nitrate | 63 | 65 |

*Fall of ⩽20% of initial measurement.
**Heart rate ⩽50 beats/min.
†⩽50 beats/min.

*Table 2 Age, sex, and symptomatic presentation in the $PGI_2$ and control groups*

| Variable | $PGI_2$ (n = 67) | Control (n = 68) |
|---|---|---|
| Mean age (SD) (yr) | 56 (8) | 53 (8) |
| M/F | 55/12 | 60/8 |
| Angina grade*: | | |
| 0 | 0 | 0 |
| 1 | 0 | 0 |
| 2 | 21 | 23 |
| 3 | 26 | 24 |
| 4 | 20 | 21 |
| Angina syndrome†: | | |
| S | 39 | 37 |
| US | 22 | 23 |
| PMI | 6 | 8 |
| Duration: | | |
| >3 mnth | 25 | 26 |
| <3 mnth | 42 | 42 |
| Mean (SD) | 9·2 (10·5) | 8·8 (12·7) |

*Canadian Cardiovascular Society Classification.
†S, stable; US, unstable; PMI, postmyocardiol infarction.

BASELINE COMPARISON BETWEEN GROUPS

One hundred and thirty five patients therefore had successful angioplasty and completed the 36 h intravenous infusion: 67 in the treatment group and 68 in the placebo group.

There were no significant differences between the groups in terms of baseline characteristics (tables 2 and 3). The two groups were similar for mean age; proportion of men; spectrum of angina grade; numbers of patients with stable, unstable, or post-infarct angina; duration of angina (mean 9·2 months $PGI_2$ group and 8·8 months placebo group); and number of patients in each group who were past or current smokers or who had a history of hypertension or diabetes. (table 3). Admission medication was not significantly different in the two groups, and 55 of 67 in the $PGI_2$ group and 60 of 68 in the placebo group received aspirin during the six month follow up period. The target vessels were similar in both groups. Table 4 shows

*Table 3 Comparison of lesion and patient factors in the $PGI_2$ and control groups*

| Factor | $PGI_2$ (n = 67) | Control (n = 68) |
|---|---|---|
| Smokers: | | |
| Never | 16 | 14 |
| Ex/current | 40 | 44 |
| Hypertension | 10 | 7 |
| Diabetes | 2 | 1 |
| Admission medication: | | |
| BB | 47 | 40 |
| CA | 42 | 43 |
| N | 49 | 44 |
| AS | 18 | 17 |
| D | 10 | 1 |
| Aspirin during trial | 55 | 60 |
| Lesion angioplastied single vessel disease: | | |
| LAD prox | 6 | 10 |
| LAD mid | 27 | 22 |
| Cx | 9 | 9 |
| RCA prox | 2 | 8 |
| RCA mid | 9 | 4 |
| RCA distal | 2 | 2 |
| Single angioplasty | 55 | 55 |
| Double angioplasty | 12 | 13 |

BB, β-blockers; CA, calcium antagonist; N, oral nitrate; A, aspirin; D, dipyridamole.

*Table 4 Outcome of exercise stress tests in the $PGI_2$ and control groups before admission*

| *Exercise stress tests before trial* | *$PGI_2$ (n = 67)* | *Control (n = 68)* |
|---|---|---|
| No. undertaken* | 48 | 42 |
| Mean stage achieved | 3·5 | 3·3 |
| Mean heart rate | 115 | 111 |
| Positive tests (>1 mm ST depression/angina) | 41 | 35 |
| Negative tests | 7 | 7 |

*No stress tests were undertaken in patients with unstable angina.

the exercise test data before angioplasty in the two groups. The number of positive tests and exercise stage achieved on admission were similar in the two groups.

Fifty five patients in each group underwent single vessel angioplasty. A further 12 in the $PGI_2$ group and 13 in the placebo group had double vessel angioplasty.

PATIENT OUTCOME

Figure 1 shows patient progress during the six month trial. Three patients died during the follow up period, one from cardiac causes (myocardial infarction at home four days after PTCA) and two from non-cardiac causes (one carcinoma of the liver and one adenocarcinoma of the lung). All three were in the placebo group. Twenty-three patients were admitted because of angina during the six month follow up (15 $PGI_2$, eight placebo). Fifteen (10 $PGI_2$, five placebo) were shown on subsequent quantitative angiography to have restenosis according to the NHLBI definition (IV). Three of the 23 patients admitted early proceeded straight to coronary surgery with no further angiogram (two $PGI_2$, one placebo) and five (three $PGI_2$, two placebo) of the 23 were thought on qualitative assessment of the angiogram at the time to not have developed restenosis. This was confirmed in all five by subsequent measurement with quantitative angiography. (Since the end point was the development of angina sufficient to warrant re-admission and need for cardiac catheterisation these patients were excluded for ethical reasons from planned further catheterisation at six months). At six months a further four patients (all placebo group) refused the follow up angiogram.

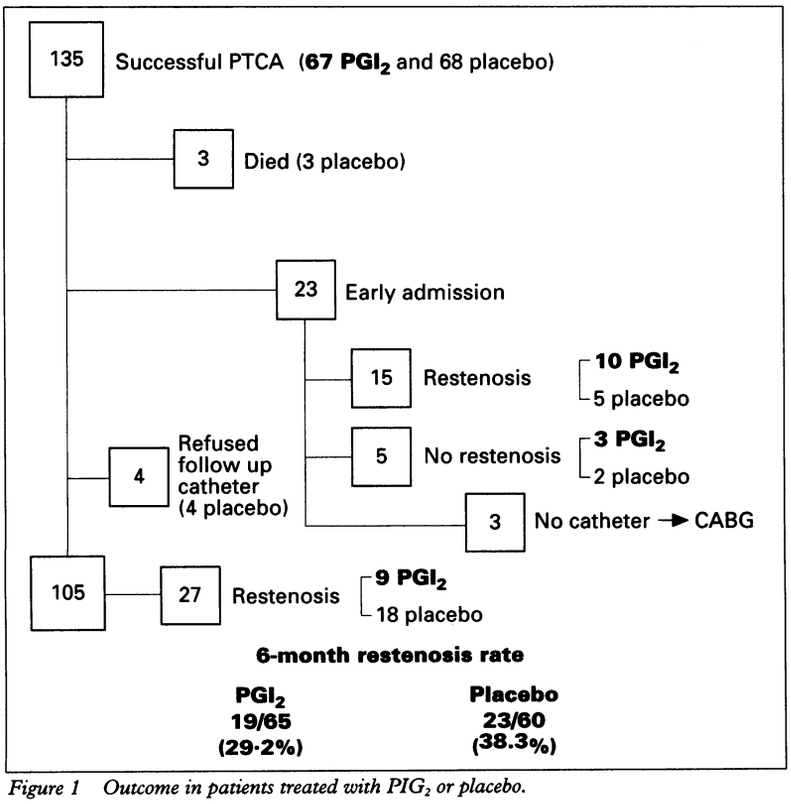


*Figure 1 Outcome in patients treated with $PIG_2$ or placebo.*

RESTENOSIS

Ten patients treated with $PGI_2$ had restenosis and were readmitted early as were five who received placebo. There were 105 other patients who were routinely admitted at mean 6·1 month (range 5·3–6·8 months) and who had follow up angiograms. This represents an overall 93% angiographic follow up. Twenty seven of the 105 patients had restenosis of at least one lesion according to definition IV (nine $PGI_2$, 18 placebo). The overall patient restenosis rate (including early admission) for the $PGI_2$ group was thus 19/65 (29·2%) *v* 23/60 (38·3%) for the placebo group (difference not significant) (fig 1).

LESION RESTENOSIS

Of the twenty-three patients who were readmitted early, two of eight in the placebo group had had double vessel angioplasty (one had no restenosis in either lesion by either definition and one had restenosis in both lesions according to both definitions for one lesion and by only the NHLBI definition IV for the other lesion—this patient underwent repeat PTCA to both lesions). Of the fifteen patients who had had active treatment and had been admitted early, only one had double

*Table 5 Mean absolute diameters (SD) (mm) for normal reference and stenotic segments*

| | *$PGI_2$* | *Control* |
|---|---|---|
| Before angioplasty: | | |
| Stenotic diameter | 0·64(0·48) | 0·63(0·52) |
| Normal diameter | 3·29(0·62) | 3·16(0·77) |
| After angioplasty: | | |
| Stenotic diameter | 2·48(0·57)* | 2·21(0·59) |
| Normal diameter | 3·14(0·68) | 2·95(0·71) |
| Six month follow up: | | |
| Stenotic diameter | 1·83(0·88) | 1·59(0·92) |
| Normal diameter | 2·92(0·66) | 2·75(0·60) |

*p = 0·04.

*Table 6 Clinical outcome in the $PGI_2$ and control groups at six months*

| | *$PGI_2$ (n = 52)* | *Control (n = 53)* |
|---|---|---|
| Angina grade at six months: | | |
| 0 | 41 | 37 |
| 1 | 7 | 12 |
| 2 | 2 | 4 |
| 3 | 1 | 0 |
| 4 | 1 | 0 |
| Exercise tests at 6 months: | | |
| No. undertaken | 51 | 53 |
| Mean stage achieved | 4·0 | 4·4 |
| Mean heart rate | 135 | 141 |
| Positive tests (>1mm ST depression/angina) | 8 | 6 |

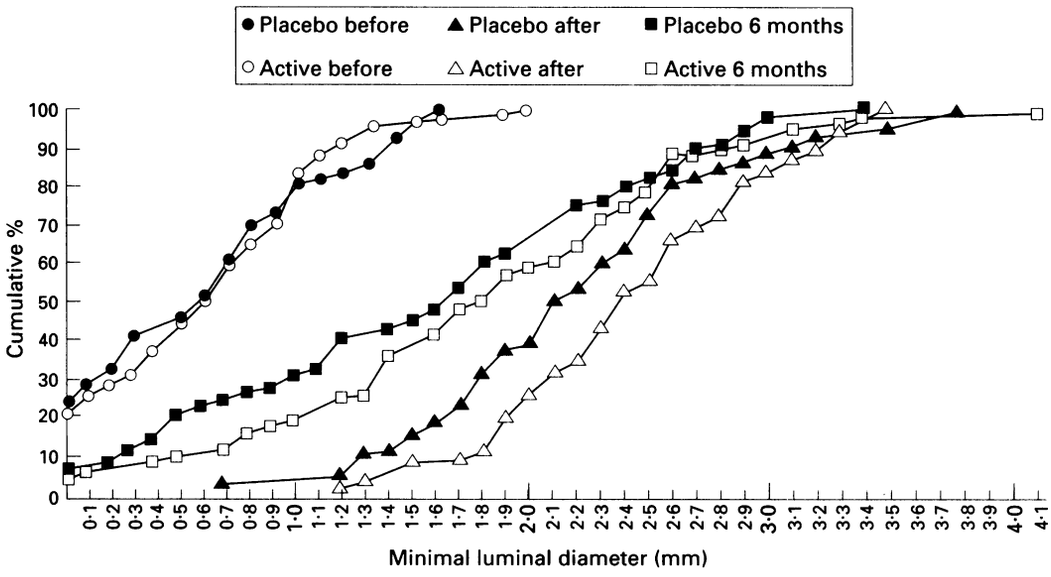


*Figure 2 Cumulative percentage plotted against minimal luminal diameter for the $PGI_2$ and placebo groups before PTCA, after PTCA, and at 6 month follow up.*

vessel disease this was diagnosed as restenosis of both lesions by both definitions.

The overall lesion restenosis rate was 22/79 (28%) for the $PGI_2$ group and 22/81 (27%) for control group.

ABSOLUTE MEASUREMENTS

Plotting the data for the cumulative incidence against the absolute diameter showed no obvious difference between the groups at follow up (fig 2). It is clear, however, that the mean post-stenotic diameter is different in the two groups (2·48 (0·57) mm *v* 2·21 (0·59) mm, p = 0·01). Thus the absolute gain was 1·84 (0·76) mm in the $PGI_2$ group and 1·58 (0·56) in the placebo group (p = 0·04). The relative gain (absolute gain/reference artery size) was also greater in the $PGI_2$ group 0·61 (0·20) *v* 0·56 (0·18) (NS). The absolute loss and relative loss in the $PGI_2$ group were however, also greater than in the placebo group although not significantly. Thus there was no significant difference between the actual minimal luminal diameters at follow up between the two groups (1·83 (0·88) mm *v* 1·59 (0·60) mm).

Table 5 shows the mean quantitative angiographic data for all lesions and fig 3 shows the absolute and relative acute gain and late loss.

CLINICAL OUTCOME

Table 6 shows the angina grade and exercise stress test results. At the six month follow up

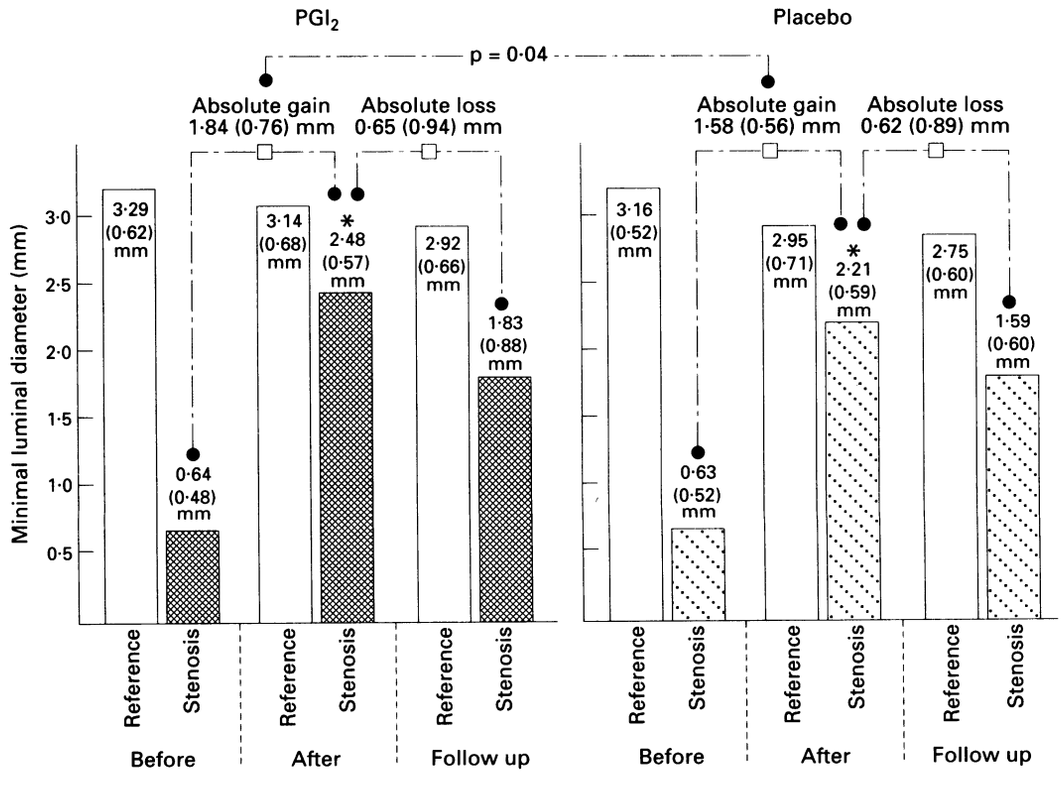


*Figure 3 Minimal luminal diameter in reference arteries (SD) and stenotic segments in the $PGI_2$ and placebo groups before PTCA, after PTCA, and at follow up. *p = 0·04 for absolute change post PTCA in $PGI_2$ group v absolute change post PTCA in placebo group.*

both groups showed a considerable improvement in both angina grade and exercise achieved (tables 2 and 4).

PLATELET DATA: AGGREGOMETRY

The 7F NIH catheter was the best one for sampling the coronary sinus from the leg. It was difficult to take samples from end hole catheters. A catheter was positioned correctly in only 24 patients in the $PGI_2$ group and 26 in the placebo group. In a further six patients in the $PGI_2$ group and three in the placebo group angioplasty took so long that the samples could not be transported to the haematology laboratory, be processed, and aggregometry performed within 2 h. These samples were discarded. Two of us (AHG and DSC) performed all the platelet function tests without knowledge of randomisation group.

In the placebo group the platelet activation index in samples taken from coronary sinus after angioplasty (CS2) was significantly higher than in samples from the aorta (A2) (11·2 (4·3) *v* 7·6 (2·8) p = 0·001: mean difference 3·8 (−5·89 to 1·86). The index was also higher than in coronary sinus samples taken before angioplasty. (CS2 *v* CS1 (7·4 (3·6)); p < 0·001 (mean difference = −4·02 (−5·91 to −2·06)). There was no significant difference between the indices in aortic samples taken before and after angioplasty (A1 7·6 (3·3 *v* A2 7·6 (2·8)).

The aggregometry results in the $PGI_2$ group were similar, with the mean platelet activation index (PAI) of 12·9 in coronary sinus samples taken after angioplasty. This value was significantly higher than the PAI of blood taken from the coronary sinus before angioplasty (CS1 8·8 (4·0), p < 0·001; mean difference −3·7 (−5·1 to −2·4)) and higher than that of aortic samples taken after angioplasty (A2 8·9 (3·0), p < 0·001; mean difference −3·60 (−5·17 to −2/04).

The concentration of 6-Keto-$PGF_{1\alpha}$ in blood taken from aortic and coronary sinus samples in the $PGI_2$ patients was significantly higher than that in the controls (mean 182·5 (66·2) pg/ml *v* < 2 pg/ml, p = < 0·001).

## Discussion

Restenosis after angioplasty is thought to be the consequence of a complex interaction between blood factors, particularly platelets and the injured blood vessel wall. The complexity of the process may explain why so-called antiplatelet drugs such as aspirin[26] (which inhibits predominantly only one of the many intraplatelet metabolic pathways[27] do not affect restenosis. Other agents such as fish oils, steroids, angiotensin converting enzyme inhibitors, and antiplatelet-derived growth factor drugs such as trapidil[28] have also been tried in an attempt to reduce restenosis by pharmacological means. We considered that it was appropriate to investigate an agent that, in theory, affects intraplatelet pathways to a greater degree than aspirin and one that is reported to influence adhesion as well as aggregation, which aspirin does not. Epoprostenol ($PGI_2$), which has been shown to increase intraplatelet cAMP and to inhibit both aggregation and adhesion[29 30] in vitro and in animal models, seemed to be a reasonable candidate. The fact that normally it is concentrated in endothelial cells, a layer consistently shown to be removed during angioplasty, also made it theoretically attractive.

Epoprostenol ($PGI_2$) was thus started before angioplasty and given for 36 h thereafter. The time period was based on work of Mustard and his group, who showed that if platelets could be kept away from a damaged surface for 36 to 48 hours, smooth muscle cell proliferation might be reduced.[31] This fitted conveniently with the fact that when the trial started $PGI_2$ could only be given intravenously and patients were routinely discharged 48 hours after angioplasty.

The $PGI_2$ and placebo treated groups had similar baseline demographic features. The mean post-angioplasty minimal luminal diameter in the $PGI_2$ group was significantly higher than that in the placebo group. This should put the $PGI_2$ group at an advantage, just as the larger minimal diameter obtained with stents may advantage such patients.

The follow up rate for early symptom-related and late follow up angiography was high (93%) with quantitative analysis and assessment of restenosis based on two definitions that represented different philosophies. The trial was designed to evaluate the efficacy of $PGI_2$ in preventing restenosis after angioplasty. In an attempt to explain any pathophysiological effects we also measured platelet function.

ANALYSIS OF RESULTS

An intravenous infusion of $PGI_2$ given from before and for 36 h after angioplasty did not significantly reduce the incidence of restenosis as measured by six month quantitative angiography.

A plot of the absolute value against the cumulative incidence showed no obvious difference between the two groups at follow up. This method has become one way of presenting such trial data. Our data confirm the current concept of "the more you gain the more you lose" because there was no difference in the late minimal luminal diameters between the two groups. Our acute gain for both groups was higher than normally reported in other trials. This may reflect our undeclared policy at that time of only performing angioplasty to larger vessels (our mean reference diameters were 3 mm +) and/or our determination to achieve a satisfactory result.

REASONS FOR APPARENT FAILURE OF $PGI_2$ TO REDUCE RESTENOSIS OR IMPROVE ABSOLUTE LUMINAL VALUE AT FOLLOW UP

*Study power*

The power of the trial might have been too low to detect the difference in restenosis reduction that would now be thought achievable. None the less, there was a 24% reduction in restenosis rate. Most current

trials are evaluating drugs in the expectation of achieving an event reduction of 30% or less.[25] Detection of a 30% event reduction, be it binary (yes/no) restenosis rate or reduction in absolute late loss, requires a minimum of 230 patients per group and detection of an event reduction of 50% requires 73 patients per group. A lowered expectation (an arbitrary 30% rather than our 50%) was based on the difficulty in finding an agent that affects restenosis, which is a process that is proving to be extremely powerful biologically. At the start of this trial, however, a reduction from a mean restenosis rate of 36% (based on trial results available at that time) to 18% was deemed reasonable with the theoretically powerful agent we were testing. Whether in general one should aim for less of an effect (that is, a reduction of 30%) or try more powerful agents is a matter for debate. With an agent such as $PGI_2$ which may have significant side effects, it is clear that the potential benefit should outweigh the disadvantages. With powerful drugs one could argue for a target of a 50% event reduction, especially because 60–70% of patients do not restenose and would be receiving the agent for no good reason.

Though there was some initial patient dropout the numbers in each group would still have detected a 50% reduction in restenosis at 80% trial power. Our trial was set up to detect a 50% reduction and this may be the reason why a lesser benefit could not be demonstrated. However, other aspects of this study suggest that-$PGI_2$ in the doses infused did not significantly alter the basic biological process.

*Platelet function tests*

This is the first study that has attempted to show a change in platelet function as a consequence of treatment during PTCA. We used ex vivo platelet aggregometry as a test of the platelet/vessel wall interaction because it is cheap, reproducible, and has been shown to be affected by $PGI_2$ in other circumstances.[17] Aggregometry can be quantitated in several ways. We used a dose response curve to calculate the platelet activation index for a standardised platelet count. This has been validated in other models of the platelet vessel wall interaction[18] and is based on the concept that not all platelets that come into contact with a damaged vessel wall stick to it. Other tests of platelet function such as platelet factor 4, $\beta$ thromboglobulin, and thromboxane $A_2$ generation have often been difficult to intepret because of the wide variance in normal valves between patients and between laboratories.[32] Others have assessed the effect of angioplasty on platelet function but in fewer patients.[33 34] A direct effect of angioplasty on ex vivo aggreometry has not been previously shown.

Our data clearly demonstrate that after angioplasty platelets in the coronary sinus are more sensitive to ex vivo aggregating agents. $PGI_2$ given in the trial dose did not however, inhibit the process. $PGI_2$ has both antiaggregatory and antiadhesion properties: the antiadhesion properties are twenty times less powerful than the antiaggregating properties.[35] Because there was non demonstrable effect on aggregation it is unlikely that the intimate contact between adherent platelets and the damaged vessel was being inhibited. We believe that this adhesion is important in restenosis because it leads to the local release of platelet-derived growth factor. While it is possible that at the time of sampling there was not enough $PGI_2$ in the circulation, all patients had received at least 10 minutes of infusion before sampling and aggregometry was undertaken within 2 h.

In this study the presence of $PGI_2$ measured as 6-keto-$PGF_{1a}$ in the coronary sinus of those patients given active treatment confirms our contention that $PGI_2$ was there, but in the dose given not powerful enough to limit platelet adherence. The dose used in this study was based on other studies in which it had been noted that frequent side effects occurred with doses of 5 ng/kg/hour or greater.[36] Even with a dose chosen to limit side effects, we found that the incidence of recognised side effects was higher in patients treated with $PGI_2$. It is likely that the vessel wall damage is such that drugs with a greater effect on adhesion (such as monocolonal antibodies against glycoprotein 1b) are required to counteract the adhesive properties of local type III collagen. Any agent designed to prevent such interactions should be present at the time of angioplasty and may need to be targeted locally to reduce the impact of powerful systemic side effects.[37]

Many agents have now been tested for their effect on restenosis. To date none, including aspirin at any dose, fish oils, steroids, thromboxane synthetase inhibitors, and thromboxane receptor blockers have consistently been shown to be of benefit. $PGI_2$ has been assessed in previous trials[38] over short infusion periods with initially similar results to this study. A recent review by Raizner *et al* has, however, revised these results.[39] This group confirmed that patients randomised to Ciprostene had better clinical outcome at six months than control group (clinical events 23% *v* 39%, $p = 0{\cdot}004$). Reanalysis of the data derived from quantitative angiography now suggests that the late loss may have been significantly less for the ciprostene group (0·32 (0·07) *v* 0·57 (0·08) mm, $p = 0{\cdot}025$). These data support the contention that $PGI_2$ given during angioplasty may be having some effect, although Raizner *et al* were only able to retrieve 83% of treated and 88% of control angiograms. Our data indicate that this group's contention that "Ciprostene warrants consideration was adjunctive treatment for the prevention of restenosis in PTCA" is not yet confirmed.

The only "antiplatelet" approach that has been successful so far reducing intimal hyperplasia has been to make animals severely thrombocytopenic.[40] If such a significant degree of platelet change is required then limiting restenosis will prove difficult.

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